LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222 • FAX (516) 683-1887

2889 '00 AUG 22 A9:04

August 18, 2000

OVERNIGHT COURIER 8/18/00

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and, in accordance with 21 CFR 10.30, on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Sertraline Hydrochloride Capsules equivalent to 25 mg, 50 mg and 100 mg of Sertraline, are suitable for consideration in abbreviated new drug applications (ANDAs).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Sertraline Hydrochloride Capsules equivalent to 25 mg, 50 mg and 100 mg of Sertraline are suitable for submission as ANDAs. The reference-listed drug product upon which this petition is based is Zoloft® Tablets (Sertraline Hydrochloride), equivalent to Sertraline 25 mg, 50 mg or 100 mg. Therefore, the petitioner seeks a change in dosage form (from tablet to capsule) from that of the listed drug product.

B. Statement of Grounds

The reference-listed drug (RLD) product is a tablet product containing 25 mg, 50 mg or 100 mg base equivalent of Sertraline Hydrochloride. The proposed drug product represents a capsule dosage form of the exact same strengths and same active ingredients as the reference-listed drug product. The petition is thus seeking a change in dosage form (from tablet to capsule) from that of the referenced-listed drug.

00P-1468

CP1

In support of the change in dosage form requested in this petition, the petitioner would like to point out that the Agency has previously approved ANDA suitability petitions allowing for a change in dosage form (from capsule to tablet) in many instances. There are no proposed changes in labeling with the exception of the obvious change in dosage form sought in this petition. However, it is recognized that it may be necessary for the labeling of the proposed product to differ due to exclusivity or patent protection related to the reference-listed drug. Draft labeling for the proposed product is included in Attachment 1. A copy of the reference-listed drug product's labeling is included in Attachment 2. The petitioner is seeking this change in dosage form in an effort to make an alternate dosage form (capsule) available for those individuals that either have difficulty in swallowing a tablet or who prefer a capsule dosage form.

In accordance with the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule (Pediatric Rule) (63 FR 66632) published December 2, 1998, the petitioner claims the following:

Sertraline has been studied in pediatric patients for the treatment of obsessive compulsive disorder (OCD). The labeling of the reference-listed drug states:

> The effectiveness of ZOLOFT for the treatment of OCD was also demonstrated in a 12-week, multi-center, parallel group study in a pediatric outpatient population (children and adolescents, ages 6-17).

In addition, the pharmacokinetics of Sertraline in the pediatric population have been defined by work of the innovator. This is evident in the reference-listed drug product's labeling which states:

> **Pediatric Pharmacokinetics** --Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of depression or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic Sertraline dosing, Sertraline was triturated up to 200 mg / day and maintained at that dose for a minimum of 11 days. On the final day of Sertraline 200 mg / day, the 6-12 year old group exhibited a mean Sertraline AUC (0-24 hr.) of 3107 ng-hr / mL, mean Cmax of 165 ng / mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean Sertraline AUC (0-24 hr.) of 2296 ng-hr / mL, mean Cmax of 123 ng / mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg / day Sertraline and exhibited a mean Sertraline AUC (0-24 hr.) of 2570 ng-hr / mL, mean Cmax of 142 ng / mL, and mean half-

life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 years olds showed about 22% lower AUC (0-24 hr.) and Cmax values when plasma concentration was adjusted for weight. This data suggests that pediatric patients metabolize Sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels.

The product does have pediatric indications in accordance with that of the reference-listed drug product. Any ultimate approval of a product based on this petition would not:

A) Represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the age group not covered in existing labeling [Note; that the labeling does address pediatric use of this product for OCD and fully describes the pharmacokinetic performance of the drug product in pediatric patients.].

B) Due to the fact that this product simply represents a different solid oral dosage form (capsule vs. tablet) and not a dosage form that would promote the use of this product in pediatric patients (i.e., oral solution or chewable tablet), it is not likely to be used in a substantial number of patients in that age group in place of the existing tablet and merely represents a convenience for patients unable to swallow tablets or who prefer capsules. The usage in the pediatric population would not be expected to change at all. In addition, it is believed that the spirit of the FDAMA and the resultant regulations implementing the requirements for sponsors to address pediatric studies for Product changes clearly sought a firm to address the formulation of drug products that would be more likely to be used and targeted for pediatric patients.

C) The absence of adequate labeling for this similar solid oral dosage form (capsule) could not pose any additional risks to pediatric patients.

Therefore, in accordance with the concepts embodied in the pediatric final rule, the petitioner requests a waiver under 21 CFR 201.23 for the need to conduct pediatric studies. The waiver is requested in accordance with the citation reference above. The reference product labeling contains the appropriate dosing recommendations for the pediatric age group for which the product is indicated. It is the petitioner's belief that the introduction of a capsule dosage form will not create any additional usage in the existing pediatric population for whom the product is recommended and based on the labeled indications will not likely be used in any additional sub-age group of pediatric patients than would the approved tablet.

If, however, for some reason the Agency determines that a waiver is not appropriate in this instance, the petitioner asks the Agency to consider the following request for deferral:

In addition to the indications approved for pediatric patients in the labeling of the reference-listed drug product's labeling and in accordance with the studies outlined above, the FDA has issued a written request for the conduct of pediatric studies to the manufacturer of the reference-listed drug product (Attachment 3). The issuance of such a written request by the Agency is, if past precedent can be used as an example, an indication that pediatric studies will be conducted and submitted to the Agency in an effort to secure an additional period of 180-days of market protection. Should the requested studies be submitted which resulted in a finding that labeled indications should be further revised to address the findings, or that based on those findings that pediatric use other than that already approved be included in labeling, the petitioner's client will appropriately revise its labeling to be in conformance with any new labeling for the reference-listed drug product.

Because it is likely that pediatric studies will be conducted prior to approval of this suitability petition, and if not certainly by the time an ANDA could be approved for a capsule version of Sertraline Hydrochloride Capsules, the petitioner requests a **deferral** for submission of a pediatric plan or the need to conduct such studies prior to approval for this drug product. There is an important public health reason for granting such a deferral. Since it appears that the innovator has or will be conducting the studies deemed appropriate to address the pediatric final rule, it would make little sense and would not be in the public health interest of any party to subject additional pediatric patients to needless drug exposure by initiating duplicative pediatric studies to demonstrate what will already be known by the Agency.

Therefore, the petitioner's requested the Commissioner to find that a change in dosage form from tablet to capsule for Sertraline Hydrochloride 25 mg, 50 mg and 100 mg should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

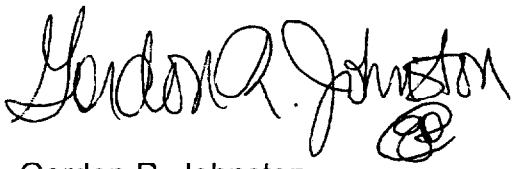
D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Gordon R. Johnston
Associate
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

GJ/gd

Attachments: Draft Labeling

cc: Greg Davis (OGD)
Leon Lachman, Ph.D. (LCS)

36k231b

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

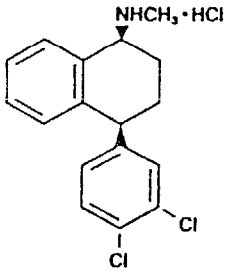
ATTACHMENT

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

ZOLOFT® TABLETS/ORAL CONCENTRATION (PFIZER)

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula C 17 H 17 NCl 2 ·HCl is represented by the following structural formula:

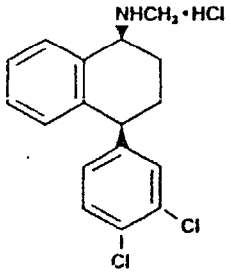


SERTRALINE HYDROCHLORIDE CAPSULES

Rx only

DESCRIPTION

Sertraline hydrochloride is a selective serotonin Reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. Sertraline hydrochloride is chemically designated: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride and has the following structural formula:



$C_{17}H_{17}NCl_2 \cdot HCl$ M.W. 342.7

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.	Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.
ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.	Sertraline Hydrochloride Capsules, for oral administration, contain sertraline hydrochloride equivalent to 25, 50 or 100 mg of sertraline and have the following inactive ingredients: **TO BE DETERMINED**
ZOLOFT oral concentrate is available in a multidose 60 mL bottle. Each mL of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS , Information for Patients and DOSAGE AND ADMINISTRATION).	

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro studies have shown that sertraline has no significant affinity for adrenergic (alpha$_1$, alpha$_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other clinically effective antidepressants. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability

In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha$_1$, alpha$_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other clinically effective antidepressants. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability

In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.	week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline capsules is approximately equal to an equivalent dose of solution.
In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and C_{max} values were 114.8% and 120.6%, respectively, 90% confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for C_{max} which was 126.5%.	
The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food.	The effects of food on the bioavailability of sertraline were studied in subjects administered a single dose with and without food. AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration decreased from 8 hours post-dosing to 5.5 hours.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Metabolism Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both in vitro biochemical and in vivo pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.	***Metabolism*** Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is *N*-demethylation. *N*-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown *N*-desmethylsertraline to be substantially less active than sertraline. Both sertraline and *N*-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.
Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), C_{max} and C_{min}, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.	Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), C_{max} and C_{min}, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.
Protein Binding In vitro protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see	***Protein Binding*** *In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and *N*-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

PRECAUTIONS).

Pediatric Pharmacokinetics
Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of depression or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean C_{max} of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean C_{max} of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean Cmax of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 years olds showed about 22% lower AUC (0-24 hr) and Cmax values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid

PRECAUTIONS).

Pediatric Pharmacokinetics
Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of depression or obsessive-compulsive disorder. Patients included both males (*n*=28) and females (*n*=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean C_{max} of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean C_{max} of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean C_{max} of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and C_{max} values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
excessive plasma levels (see DOSAGE AND ADMINISTRATION).	excessive plasma levels (see **DOSAGE AND ADMINISTRATION**).
Age Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.	***Age*** Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.
Liver Disease As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver	**Liver Disease** As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (*n*=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (*n*=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver impairment must be approached with caution. If sertraline is administered to patients with liver

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
effectiveness.	effectiveness.
Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on ZOLOFT 50-200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind ZOLOFT 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking ZOLOFT compared to those on placebo. The mean dose for completers was 70 mg/day.	Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (*n*=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day.
Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.	Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex.
Obsessive-Compulsive Disorder (OCD) The effectiveness of ZOLOFT in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.	**Obsessive-Compulsive Disorder (OCD)** The effectiveness of sertraline in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III or DSM-III-R) with mean baseline ratings on the Yale Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.
Study 1 was an 8-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo-treated patients.	Study 1 was an 8-week study with flexible dosing of sertraline in a range of 50 to 200 mg/day; the mean dose for completers was 186 mg/day. Patients receiving sertraline experienced a mean reduction of approximately 4 points on the YBOCS total score which was significantly greater than the mean reduction of 2 points in placebo-treated patients.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Study 2 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the YBOCS total score which were significantly greater than the approximately 3 point reduction in placebo-treated patients.	Study 2 was a 12-week fixed-dose study, including sertraline doses of 50, 100, and 200 mg/day. Patients receiving sertraline doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the YBOCS total score which were significantly greater than the approximately 3 point reduction in placebo-treated patients.
Study 3 was a 12-week study with flexible dosing of ZOLOFT in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Patients receiving ZOLOFT experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.	Study 3 was a 12-week study with flexible dosing of sertraline in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Patients receiving sertraline experienced a mean reduction of approximately 7 points on the YBOCS total score which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.
Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.	Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.
The effectiveness of ZOLOFT for the treatment of OCD was also demonstrated in a 12-week, multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 6-17). Patients in this study were initiated at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe	The effectiveness of sertraline for the treatment of OCD was also demonstrated in a 12-week, multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 6-17). Patients in this study were initiated at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-17), and then titrated over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe

INNOVATOR'S INSERT LABELING	S PROPOSED INSERT LABELING
OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 units on the CYBOCS total score which was significantly greater than the 3 unit reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.	OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 units on the CYBOCS total score which was significantly greater than the 3 unit reduction for placebo patients. Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.
Panic Disorder The effectiveness of ZOLOFT in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1-3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.	**Panic Disorder** The effectiveness of sertraline in the treatment of panic disorder was demonstrated in three double-blind, placebo-controlled studies (Studies 1-3) of adult outpatients who had a primary diagnosis of panic disorder (DSM-III-R), with or without agoraphobia.
Studies 1 and 2 were 10-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, ZOLOFT was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between ZOLOFT and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.	Studies 1 and 2 were 10-week flexible dose studies. sertraline was initiated at 25 mg/day for the first week, and then patients were dosed in a range of 50-200 mg/day on the basis of clinical response and toleration. The mean sertraline doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies 1 and 2. In these studies, sertraline was shown to be significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity of Illness and Global Improvement scores. The difference between sertraline and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Study 3 was a 12-week fixed-dose study, including ZOLOFT doses of 50, 100, and 200 mg/day. Patients receiving ZOLOFT experienced a significantly greater reduction in panic attack frequency than patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.	Study 3 was a 12-week fixed-dose study, including sertraline doses of 50, 100, and 200 mg/day. Patients receiving sertraline experienced a significantly greater reduction in panic attack frequency than patients receiving placebo. Study 3 was not readily interpretable regarding a dose response relationship for effectiveness.
Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.	Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender.
Posttraumatic Stress Disorder (PTSD) The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.	**Posttraumatic Stress Disorder (PTSD)** The effectiveness of sertraline in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.
Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event	Studies 1 and 2 were 12-week flexible dose studies. sertraline was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50-200 mg/day on the basis of clinical response and toleration. The mean sertraline dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of reexperiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.	Scale (IES) which measures intrusion and avoidance symptoms. sertraline was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving sertraline and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.
As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid depression, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.	As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between sertraline and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid depression, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
INDICATIONS AND USAGE Depression ZOLOFT® (sertraline hydrochloride) is indicated for the treatment of depression.	**INDICATIONS AND USAGE** **Depression** Sertraline Hydrochloride Capsules are indicated for the treatment of depression.
The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).	The efficacy of sertraline in the treatment of a major depressive episode was established in six to eight week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see **CLINICAL PHARMACOLOGY, Clinical Trials**).
A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.	A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.
The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.	The antidepressant action of sertraline in hospitalized depressed patients has not been adequately studied.
The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be	The efficacy of sertraline in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving sertraline for extended periods should be

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).	reevaluated periodically (see **CLINICAL PHARMACOLOGY, Clinical Trials**).
Obsessive-Compulsive Disorder ZOLOFT is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.	**Obsessive-Compulsive Disorder** Sertraline Hydrochloride Capsules are indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.
The efficacy of ZOLOFT was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see Clinical Trials under CLINICAL PHARMACOLOGY).	The efficacy of sertraline was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see **CLINICAL PHARMACOLOGY, Clinical Trials**).
Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.	Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.
The effectiveness of ZOLOFT in long-term use for OCD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).	The effectiveness of sertraline in long-term use for OCD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use sertraline for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Panic Disorder ZOLOFT is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.	**Panic Disorder** Sertraline Hydrochloride Capsules are indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.
The efficacy of ZOLOFT was established in three 10-12 week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).	The efficacy of sertraline was established in three 10-12 week trials in panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).
Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. The effectiveness of ZOLOFT® (sertraline hydrochloride) in long-term use, that is, for more than 12 weeks, has not been systematically evaluated in controlled trials.	Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. The effectiveness of sertraline® (sertraline hydrochloride) in long-term use, that is, for more than 12 weeks, has not been systematically evaluated in controlled trials.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Therefore, the physician who elects to use ZOLOFT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).	Therefore, the physician who elects to use sertraline for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).
Posttraumatic Stress Disorder (PTSD) ZOLOFT (sertraline hydrochloride) is indicated for the treatment of posttraumatic stress disorder. The efficacy of ZOLOFT in the treatment of PTSD was established in two 12-week placebo-controlled trials of outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see Clinical Trials under CLINICAL PHARMACOLOGY).	**Posttraumatic Stress Disorder (PTSD)** Sertraline Hydrochloride Capsules are indicated for the treatment of posttraumatic stress disorder. The efficacy of sertraline in the treatment of PTSD was established in two 12-week placebo-controlled trials of outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see **CLINICAL PHARMACOLOGY, Clinical Trials**).
PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror.	PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror.
Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle	Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
The effectiveness of ZOLOFT in long-term use for PTSD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials; therefore, the physician who elects to use ZOLOFT for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).	The effectiveness of sertraline in long-term use for PTSD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials; therefore, the physician who elects to use sertraline for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).
CONTRAINDICATIONS All Dosage Forms of ZOLOFT: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).	**CONTRAINDICATIONS** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).
Oral Concentrate: ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.	
WARNINGS Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT® (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia,	WARNINGS **Cases of serious sometimes fatal reactions have been reported in patients receiving sertraline, a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia,**

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.	**rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, sertraline should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping sertraline before starting an MAOI.**
PRECAUTIONS General Activation of Mania/Hypomania During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT® (sertraline hydrochloride) treated patients.	PRECAUTIONS **General** **Activation of Mania/Hypomania** During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline treated patients.
Weight Loss Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.	**Weight Loss** Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.
Seizure ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies	**Seizure** Sertraline has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
during the product' premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for depression. However, 4 patients out of approximately 1800 (220 <18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, ZOLOFT should be introduced with care in patients with a seizure disorder.	during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with sertraline in the development program for depression. However, 4 patients out of approximately 1800 (220 <18 years of age) exposed during the development program for a disorder other than depression experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, sertraline should be introduced with care in patients with a seizure disorder.
Suicide The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.	**Suicide** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for sertraline should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.
Because of the well-established comorbidity between OCD and depression, panic disorder and depression, and PTSD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder or PTSD.	Because of the well-established comorbidity between OCD and depression, panic disorder and depression, and PTSD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder or PTSD.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Weak Uricosuric Effect ZOLOFT® (sertraline hydrochloride) is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT.	**Weak Uricosuric Effect** Sertraline is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with sertraline.
Use in Patients with Concomitant Illness Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.	***Use in Patients with Concomitant Illness*** Clinical experience with sertraline in patients with certain concomitant systemic illness is limited. Caution is advisable in using sertraline in patients with diseases or conditions that could affect metabolism or hemodynamic responses.
ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product' premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.	Sertraline has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received sertraline in double-blind trials were evaluated and the data indicate that sertraline is not associated with the development of significant ECG abnormalities.
ZOLOFT is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, Cmax and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to	Sertraline is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, C_{max} and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).	patients with liver impairment, a lower or less frequent dose should be used (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).
Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).	Since sertraline is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetics results, there is no need for dosage adjustment in patients with renal impairment (see **CLINICAL PHARMACOLOGY**).
Interference with Cognitive and Motor Performance In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance.	**Interference with Cognitive and Motor Performance** In controlled studies, sertraline did not cause sedation and did not interfere with psychomotor performance.
Hyponatremia Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.	**Hyponatremia** Several cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.
Platelet Function There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients	**Platelet Function** There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role.	taking sertraline. While there have been reports of abnormal bleeding or purpura in several patients taking sertraline, it is unclear whether sertraline had a causative role.
Information for Patients Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT:	**Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe sertraline:
Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely.	Patients should be told that although sertraline has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely.
Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised.	Patients should be told that although sertraline has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of sertraline and alcohol is not advised.
Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to	Patients should be told that while no adverse interaction of sertraline with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast feeding an infant. ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate. ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber. Laboratory Tests None.	the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast feeding an infant. **Laboratory Tests** None

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Drug Interactions Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT® (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound ZOLOFT by other tightly bound drugs.	**Drug Interactions** **Potential Effects of Coadministration of Drugs** **Highly Bound to Plasma Proteins** Because sertraline is tightly bound to plasma protein, the administration of sertraline to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline by other tightly bound drugs.
In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.	In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either sertraline (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for sertraline compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the sertraline group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.
Cimetidine In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.	**Cimetidine** In a study assessing disposition of sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in sertraline mean AUC (50%), C_{max} (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
CNS Active Drugs In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.	**CNS Active Drugs** In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either sertraline (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the sertraline group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the sertraline group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.
In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium.	In a placebo-controlled trial in normal volunteers, the administration of two doses of sertraline did not significantly alter steady-state lithium levels or the renal clearance of lithium.
Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose.	Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of sertraline therapy with appropriate adjustments to the lithium dose.
The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required.	The risk of using sertraline in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of sertraline and such drugs is required.
There is limited controlled experience regarding the optimal timing of switching from other antidepressants to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should	There is limited controlled experience regarding the optimal timing of switching from other antidepressants to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.	intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.
Monoamine Oxidase Inhibitors See CONTRAINDICATIONS and WARNINGS .	***Monoamine Oxidase Inhibitors*** See **CONTRAINDICATIONS** and **WARNINGS.**
Drugs Metabolized by P450 3A4 In two separate in vivo interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.	***Drugs Metabolized by P450 3A4*** In two separate *in vivo* interaction studies, sertraline was coadministered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.
Drugs Metabolized by P450 2D6 Many antidepressants, e.g., the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the	***Drugs Metabolized by P450 2D6*** Many antidepressants, e.g., the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
co-administered drug. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressants under PRECAUTIONS).	coadministered drug. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with sertraline may require lower doses than usually prescribed for the other drug. Furthermore, whenever sertraline is withdrawn from co-therapy, an increased dose of the coadministered drug may be required (see **PRECAUTIONS**, ***Tricyclic Antidepressants***).
Sumatriptan There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.	**Sumatriptan** There have been rare postmarketing reports describing patient with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g. citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.
Tricyclic Antidepressants (TCAs) The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by	***Tricyclic Antidepressants (TCAs)*** The extent to which SSRI–TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with sertraline, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with sertraline (see **PRECAUTIONS**,

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
P450 2D6 under PRECAUTIONS).	*Drugs Metabolized by P450 2D6*).
Hypoglycemic Drugs In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.	*Hypoglycemic Drugs* In a placebo-controlled trial in normal volunteers, administration of sertraline for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.
Atenolol ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.	**Atenolol** Sertraline (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.
Digoxin In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.	**Digoxin** In a placebo-controlled trial in normal volunteers, administration of sertraline for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.
Microsomal Enzyme Induction Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies, ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in	**Microsomal Enzyme Induction** Preclinical studies have shown sertraline to induce hepatic microsomal enzymes. In clinical studies, sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.	antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.
Electroconvulsive Therapy There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.	**Electroconvulsive Therapy** There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and sertraline.
Alcohol Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended.	**Alcohol** Although sertraline did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of sertraline and alcohol is not recommended.
Carcinogenesis Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m 2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m 2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m 2 basis); this was not accompanied by thyroid hyperplasia.	**Carcinogenesis** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/ m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m2 basis) compared to placebo controls, this effect was not clearly drug related.	While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.
Mutagenesis Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes.	**Mutagenesis** Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.
Impairment of Fertility A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m 2 basis).	**Impairment of Fertility** A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).
Pregnancy	**Pregnancy**
Pregnancy Category C Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m 2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m 2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m 2 basis) in rabbits. When female rats received sertraline during the last third of	**Teratogenic Effects** **Pregnancy Category C** Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m 2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m 2 basis). The decrease in pup survival was shown to be due to in utero exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. ZOLOFT® (sertraline hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first four days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. Sertraline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery The effect of ZOLOFT on labor and delivery in humans is unknown.	**Labor and Delivery** The effect of sertraline on labor and delivery in humans is unknown.
Nursing Mothers It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.	**Nursing Mothers** It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sertraline is administered to a nursing woman.
Pediatric Use The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see Clinical Trials under CLINICAL	**Pediatric Use** The efficacy of sertraline for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see **CLINICAL PHARMACOLOGY, Clinical**

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
PHARMACOLOGY). The effectiveness of ZOLOFT in pediatric patients with depression or panic disorder has not been systematically evaluated.	**Trials**). The effectiveness of sertraline in pediatric patients with depression or panic disorder has not been systematically evaluated.
Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with depression or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).	Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with depression or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).
More than 250 patients with depression or OCD between 6 and 17 years of age have received ZOLOFT in clinical trials. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.	More than 250 patients with depression or OCD between 6 and 17 years of age have received sertraline in clinical trials. The adverse event profile observed in these patients was generally similar to that observed in adult studies with sertraline (see **ADVERSE REACTIONS**). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of sertraline. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.
The risks, if any, that may be associated with sertraline' extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth,	The risks, if any, that may be associated with sertraline' extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth,

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.	development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.
Geriatric Use Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients.	**Geriatric Use** Several hundred elderly patients have participated in clinical studies with sertraline. The pattern of adverse reactions in the elderly was similar to that in younger patients.
ADVERSE REACTIONS During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 26, 1998. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including depression, OCD, panic disorder and PTSD.	**ADVERSE REACTIONS** During its premarketing assessment, multiple doses of sertraline were administered to over 4000 adult subjects as of February 26, 1998. The conditions and duration of exposure to sertraline varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including depression, OCD, panic disorder and PTSD.
Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that	Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.	follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of sertraline who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving sertraline. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.
The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.	The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.
Incidence in Placebo-Controlled Trials Table 1 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with depression/other*, OCD,	**Incidence in Placebo-Controlled Trials** Table 1 enumerates the most common treatment-emergent adverse events associated with the use of sertraline (incidence of at least 5% for sertraline and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with depression/other*, OCD,

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

panic disorder and PTSD in placebo-controlled clinical trials. Most patients received doses of 50 to 200 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of depression/other*, OCD, panic disorder and PTSD. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Depression/Other		OCD		Panic Disorder		PTSD	
Body System/ Adverse Event	ZOLOFT (N=861)	Placebo (N=853)	ZOLOFT (N=533)	Placebo (N=373)	ZOLOFT (N=430)	Placebo (N=275)	ZOLOFT (N =374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure [1]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
General								
Fatigue	11	8	14	10	11	6	10	5
Gastrointestinal Disorders								
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

[1] Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT depression/other*; N=271 placebo depression/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD).
*Depression and other premarketing controlled trials.

panic disorder and PTSD in placebo-controlled clinical trials. Most patients received doses of 50 to 200 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of depression/other*, OCD, panic disorder and PTSD. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Depression/Other*		OCD		Panic Disorder		PTSD	
Body System/ Adverse Event	Sertraline Hydrochloride (N=861)	Placebo (N=853)	Sertraline Hydrochloride (N=533)	Placebo (N=373)	Sertraline Hydrochloride (N=430)	Placebo (N=275)	Sertraline Hydrochloride (N=430)	Placebo (N=275)
Autonomic Nervous System Disorders								
Ejaculation Failure [1]	7	<1	17	2	19	1	11	1
Mouth dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Central & Peripheral Nervous System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Gastrointestinal Disorders								
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/ Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

(1) Primarily ejaculatory delay. Denominator used was for male patients only (*N*=271 sertraline depression/other*; *N*=271 placebo depression/other*; *N*=296 sertraline OCD; *N*=219 placebo OCD; *N*=216 sertraline panic disorder; *N*=134 placebo panic disorder, *N*=130 sertraline PTSD, *N*=149 placebo PTSD).
* Depression and other premarketing controlled trials.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Depression/Other *, OCD, Panic Disorder and PTSD combined

Body System/Adverse Event	ZOLOFT (N=2198)	Placebo (N=1877)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	15	9
Sweating Increased	6	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	14	7
Dizziness	12	7
Headache	26	24
Paresthesia	3	2
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	7	5
Diarrhea/Loose Stools	21	11
Dyspepsia	8	4
Flatulence	4	3
Nausea	27	13
Vomiting	4	2
General		
Fatigue	11	7
Hot Flushes	2	1
Psychiatric Disorders		
Agitation	6	4
Anxiety	4	3
Insomnia	22	11
Libido Decreased	6	1
Nervousness	6	4
Special Senses		
Vision Abnormal	4	2

[1] Primarily ejaculatory delay. Denominator used was for male patients only (N=913 ZOLOFT, N=773 placebo).
*Depression and other premarketing controlled trials.
**Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain and pharyngitis.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 lists the adverse events associated with discontinuation of ZOLOFT® (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in depression/other*, OCD, panic disorder and PTSD.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Percentage of Patients Reporting Event
Depression/Other*, OCD, Panic Disorder and PTSD combined

Body System/Adverse Event**	Sertraline Hydrochloride (*N*=2198)	Placebo (*N*=1877)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	15	9
Sweating Increased	6	2
Central & Peripheral Nervous System Disorders		
Somnolence	14	7
Dizziness	12	7
Headache	26	24
Paresthesia	3	2
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	7	5
Diarrhea/Loose Stools	21	11
Dyspepsia	8	4
Flatulence	4	3
Nausea	27	13
Vomiting	4	2
General		
Fatigue	11	7
Hot Flushes	2	1
Psychiatric Disorders		
Agitation	6	4
Anxiety	4	3
Insomnia	22	11
Libido Decreased	6	1
Nervousness	6	4
Special Senses		
Vision Abnormal	4	2

(1) Primarily ejaculatory delay. Denominator used was for male patients only (*N*=913 sertraline; *N*=773 placebo).
* Depression and other premarketing controlled trials.
** Included are events reported by at least 2% of patients taking sertraline except the following events, which had an incidence on placebo greater than or equal to sertraline: abdominal pain and pharyngitis.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 lists the adverse events associated with discontinuation of sertraline treatment (incidence at least twice that for placebo and at least 1% for sertraline in clinical trials) in depression/other*, OCD, panic disorder and PTSD.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Depression/Other, OCD, Panic Disorder and PTSD combined (N=2198)	Depression/Other (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)
Agitation	1%	1%	--	2%	--
Diarrhea	2%	2%	2%	1%	--
Dizziness	1%	--	1%	--	--
Dry Mouth	--	1%	--	--	--
Dyspepsia	--	--	--	1%	--
Ejaculation Failure	1%	1%	1%	2%	--
Headache	1%	2%	--	--	1%
Insomnia	2%	1%	3%	2%	--
Nausea	3%	4%	3%	3%	2%
Nervousness	--	--	--	2%	--
Somnolence	2%	1%	2%	2%	--
Tremor	--	2%	--	--	--

(1) Primarily ejaculatory delay. Denominator used was for male patients only (N=271 depression/other ; N=296 OCD; N=216 panic disorder; N=130 PTSD).
*Depression and other premarketing controlled trials.

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Depression/Other*, OCD, Panic Disorder AND PTSD combined (*N*=2198)	Depression/ Other* (*N*=861)	OCD (*N*=533)	Panic Disorder (*N*=430)	PTSD (*N*=374)
Agitation	1%	1%	-	2%	-
Diarrhea	2%	2%	2%	1%	-
Dizziness	1%	-	1%	-	-
Dry Mouth	-	1%	-	-	-
Dyspepsia	-	-	-	1%	-
Ejaculation Failure[1]	1%	1%	1%	2%	-
Headache	1%	2%	-	-	1%
Insomnia	2%	1%	3%	2%	-
Nausea	3%	4%	3%	2%	2%
Nervousness	-	-	-	2%	-
Somnolence	2%	1%	2%	2%	-
Tremor	-	2%	-	-	-

(1) Primarily ejaculatory delay. Denominator used was for male patients only (*N*=271) depression/other*; *N*=296 OCD; *N*=216 panic disorder; *N*=130 PTSD).
*Depression and other premarketing controlled trials

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

TABLE 4

Treatment	Ejaculation failure (primarily delayed ejaculation)		Decreased libido	
	N (males only)	Incidence	N (males and females)	Incidence
ZOLOFT	913	14%	2198	6%
Placebo	773	1%	1877	1%

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients
In approximately N=250 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate in a controlled trial (N=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis.

Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking sertraline in placebo-controlled clinical trials.

TABLE 4

Treatment	Ejaculatory failure (primarily delayed ejaculation)		Decreased libido	
	N (males only)	Incidence	*N* (males and females)	Incidence
Sertraline	913	14%	2198	6%
Placebo	773	1%	1877	1%

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Adverse Events in Pediatric Patients
In approximately *n*=250 pediatric patients treated with sertraline, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events, not appearing in Tables 1 and 2, were reported at a rate of at least 2% and occurred at a rate at least twice the placebo rate in a controlled trial (*n*=187): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Other Events Observed During the Premarketing Evaluation of ZOLOFT® (sertraline hydrochloride)	**Other Events Observed During the Premarketing Evaluation of Sertraline**
Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.	Following is a list of treatment-emergent adverse events reported during premarketing assessment of sertraline in clinical trials (over 4000 adults) except those already listed in the previous tables or elsewhere in labeling.
In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.	In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adults exposed to multiple doses of sertraline who experienced an event of the type cited on at least one occasion while receiving sertraline. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to sertraline treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with sertraline, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are	Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
also described in the **PRECAUTIONS** section.	also described in the **PRECAUTIONS** section.
Autonomic Nervous System Disorders Frequent: impotence Infrequent: flushing, increased saliva, cold clammy skin, mydriasis; Rare: pallor, glaucoma, priapism, vasodilation.	***Autonomic Nervous System Disorders*** *Frequent:* Impotence *Infrequent* Flushing, increased saliva, cold clammy skin, mydriasis *Rare* Pallor, glaucoma, priapism, vasodilation
Body as a Whole--General Disorders Rare allergic reaction, allergy.	**Body as a Whole-General Disorders** *Rare* Allergic reaction, allergy
Cardiovascular Frequent palpitations, chest pain Infrequent hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; Rare: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.	**Cardiovascular** *Frequent* Palpitations, chest pain *Infrequent* Hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema *Rare* Precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Central and Peripheral Nervous System Disorders Frequent hypertonia, hypoesthesia Infrequent twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; Rare dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.	**Central and Peripheral Nervous System Disorders** *Frequent* Hypertonia, hypoesthesia *Infrequent* Twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia *Rare* Dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia
Disorders of Skin and Appendages Infrequent pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash Rare: follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.	**Disorders of Skin and Appendages** *Infrequent* Pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash *Rash* Follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash
Endocrine Disorders Rare exophthalmos, gynecomastia.	**Endocrine Disorders** *Rare* Exophthalmos, gynecomastia
Gastrointestinal Disorders Frequent appetite increased Infrequent dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis	**Gastrointestinal Disorders** *Frequent* Appetite increased *Infrequent* Dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Rare: melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.	*Rare* Melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration
General Frequent back pain, asthenia, malaise, weight increase; Infrequent fever, rigors, generalized edema Rare: face edema, aphthous stomatitis.	**General** *Frequent* Back pain, asthenia, malaise, weight increase *Infrequent* Fever, rigors, generalized edema *Rare* Face edema, aphthous stomatitis
Hearing and Vestibular Disorders Rare hyperacusis, labyrinthine disorder.	**Hearing and Vestibular Disorders** *Rare* Hyperacusis, labyrinthine disorder
Hematopoietic and Lymphatic Rare anemia, anterior chamber eye hemorrhage	**Hematopoietic and Lymphatic** *Rare* Anemia, anterior chamber eye hemorrhage
Liver and Biliary System Disorders Rare abnormal hepatic function.	**Liver and Biliary System Disorders** *Rare* Abnormal hepatic function
Metabolic and Nutritional Disorders Infrequent: thirst Rare: hypoglycemia, hypoglycemia reaction.	**Metabolic and Nutritional Disorders** *Infrequent* Thirst *Rare* Hypoglycemia, hypoglycemia reaction

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Musculoskeletal System Disorders Frequent: myalgia Infrequent: arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.	**Musculoskeletal System Disorders** *Frequent* Myalgia *Infrequent* Arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness
Psychiatric Disorders Frequent: yawning, other male sexual dysfunction, other female sexual dysfunction; Infrequent: depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; Rare: withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.	**Psychiatric Disorders** *Frequent:* Yawning, other male sexual dysfunction, other female sexual dysfunction *Infrequent* Depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions *Rare* Withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion
Reproductive Infrequent menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; Rare: female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis	***Reproductive*** *Infrequent* Menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea *Rare* Female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis

INNOVATOR'S INSERT LABELING	'S PROPOSED INSERT LABELING
Respiratory System Disorders Frequent: rhinitis Infrequent: coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; Rare: hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.	**Respiratory System Disorders** *Frequent* Rhinitis *Infrequent* Coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis *Rare* Hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis
Special Senses Frequent: tinnitus Infrequent: conjunctivitis, earache, eye pain, abnormal accommodation; Rare: xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.	**Special Senses** *Frequent* Tinnitus *Infrequent* Conjunctivitis, earache, eye pain, abnormal accommodation *Rare* Xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect
Urinary System Disorders Infrequent: micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; Rare: cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.	**Urinary System Disorders** *Infrequent* Micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence *Rare* Cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury
Laboratory Tests In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with	**Laboratory Tests** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
ZOLOFT® (sertraline hydrochloride) administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.	sertraline administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.
ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.	Sertraline therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.
The safety profile observed with ZOLOFT treatment in patients with depression, OCD, panic disorder and PTSD is similar.	The safety profile observed with ZOLOFT treatment in patients with depression, OCD, panic disorder and PTSD is similar.
Other Events Observed During the Postmarketing Evaluation of ZOLOFT Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: increased coagulation times, bradycardia, AV block, atrial arrhythmias, hypothyroidism, leukopenia, thrombocytopenia, hyperglycemia, priapism, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, psychosis, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events--clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in	**Other Events Observed During the Postmarketing Evaluation of Sertraline** Reports of adverse events temporally associated with sertraline that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug include the following: increased coagulation times, bradycardia, AV block, atrial arrhythmias, hypothyroidism, leukopenia, thrombocytopenia, hyperglycemia, priapism, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, psychosis, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events - clinical features (which in the majority of cases appeared to be reversible with discontinuation of sertraline) occurring in

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.	one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.
DRUG ABUSE AND DEPENDENCE Controlled Substance Class ZOLOFT® (sertraline hydrochloride) is not a controlled substance.	**DRUG ABUSE AND DEPENDENCE** **Controlled Substance Class** Sertraline is not a controlled substance.
Physical and Psychological Dependence -- In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of ZOLOFT, alprazolam, and d-amphetamine in humans, ZOLOFT did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug linking, that were observed with the other two drugs. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies ZOLOFT does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).	**Physical and Psychological Dependence** In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of sertraline, alprazolam, and *d*-amphetamine in humans, sertraline did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs. Premarketing clinical experience with sertraline did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. In animal studies sertraline does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behavior).
OVERDOSAGE Human Experience As of November 1992, there were 79 reports of nonfatal acute overdoses involving ZOLOFT, of which 28 were overdoses of ZOLOFT alone and the remainder involved a	**OVERDOSAGE** **Human Experience** As of November 1992, there were 79 reports of nonfatal acute overdoses involving sertraline, of which 28 were overdoses of sertraline alone and the remainder involved a

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
combination of other drugs and/or alcohol in addition to ZOLOFT. In those cases of overdose involving only ZOLOFT, the reported doses ranged from 500 mg to 6000 mg. In a subset of 18 of these patients in whom ZOLOFT blood levels were determined, plasma concentrations ranged from <5 ng/mL to 554 ng/mL. Symptoms of overdose with ZOLOFT alone included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when ZOLOFT was taken alone, there were 4 deaths involving overdoses of ZOLOFT in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively.	combination of other drugs and/or alcohol in addition to sertraline. In those cases of overdose involving only sertraline, the reported doses ranged from 500 mg to 6000 mg. In a subset of 18 of these patients in whom sertraline blood levels were determined, plasma concentrations ranged from <5 ng/mL to 554 ng/mL. Symptoms of overdose with sertraline alone Included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when sertraline was taken along, there were 4 deaths involving overdoses of sertraline in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively.
Overdose Management Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.	**Overdosage Management** Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.
Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.	Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.
Activated charcoal should be administered. Due to large volume of distribution of this drug, forced diuresis,	Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis,

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.	dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR).	In managing overdosage, consider the possibility of multiple drug involvement. The Physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).
DOSAGE AND ADMINISTRATION Initial Treatment Dosage for Adults Depression and Obsessive-Compulsive Disorder ZOLOFT treatment should be administered at a dose of 50 mg once daily.	**DOSAGE AND ADMINISTRATION** **Initial Treatment** **Dosage for Adults** **Depression** Sertraline treatment should be administered at a dose of 50 mg once daily.
Panic Disorder and Posttraumatic Stress Disorder ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily. While a relationship between dose and effect has not been established for depression, OCD, panic disorder or PTSD, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1	**Panic Disorder and Posttraumatic Stress Disorder** Sertraline treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily. While a relationship between dose and effect has not been established for depression, OCD, panic disorder or PTSD, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
week.	week.
ZOLOFT should be administered once daily, either in the morning or evening.	Sertraline should be administered once daily, either in the morning or evening.
Dosage for Pediatric Population (Children and Adolescents) Obsessive-Compulsive Disorder ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6-12) and at a dose of 50 mg once daily in adolescents (ages 13-17).	**Dosage for Pediatric Population (Children and Adolescents)** **Obsessive-Compulsive Disorder** Sertraline treatment should be initiated with a dose of 25 mg once daily in children (ages 6-12) and at a dose of 50 mg once daily in adolescents (ages 13-17).
While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6-17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.	While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline for pediatric patients (6-17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of sertraline, dose changes should not occur at intervals of less than 1 week.
ZOLOFT should be administered once daily, either in the morning or evening.	Sertraline should be administered once daily, either in the morning or evening.

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Dosage for Hepatically Impaired Patients The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).	**Dosage for Hepatically Impaired Patients** The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).
Maintenance/Continuation/Extended Treatment Depression It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of ZOLOFT has shown that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY).	**Maintenance/Continuation/Extended Treatment** **Depression** It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of sertraline has shown that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see **CLINICAL PHARMACOLOGY, Clinical Trials**).
Obsessive-Compulsive Disorder, Panic Disorder and Posttraumatic Stress Disorder Although the efficacy of ZOLOFT beyond 10-12 weeks of dosing for OCD, panic disorder and PTSD has not been documented in controlled trials, all are chronic conditions, and it is reasonable to consider continuation of a responding patient. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage, and	**Obsessive-Compulsive Disorder, Panic Disorder and** **Posttraumatic Stress Disorder** Although the efficacy of sertraline beyond 10-12 weeks of dosing for OCD, panic disorder and PTSD has not been documented in controlled trials, all are chronic conditions, and it is reasonable to consider continuation of a responding patient. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage, and

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
patients should be periodically reassessed to determine the need for continued treatment.	patients should be periodically reassessed to determine the need for continued treatment.
Switching Patients to or from a Monoamine Oxidase Inhibitor At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).	**Switching Patients to or from a Monoamine Oxidase Inhibitor** At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with sertraline. In addition, at least 14 days should be allowed after stopping sertraline before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).
ZOLOFT Oral Concentrate ZOLOFT Oral Concentrate contains 20 mg/mL of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. ZOLOFT Oral Concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of ZOLOFT Oral Concentrate and mix with 4 oz (1/2 cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix ZOLOFT Oral Concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber. ZOLOFT oral concentrate is contraindicated with ANTABUSE (disulfiram) due to the alcohol content of the concentrate.	

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
HOW SUPPLIED ZOLOFT® (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles. ZOLOFT® 25 mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg. NDC 0049-4960-50 Bottles of 50 ZOLOFT® 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg. NDC 0049-4900-66 Bottles of 100 NDC 0049-4900-73 Bottles of 500 NDC 0049-4900-94 Bottles of 5000 NDC 0049-4900-41 Unit Dose Packages of 100 ZOLOFT® 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg. NDC 0049-4910-66 Bottles of 100 NDC 0049-4910-73 Bottles of 500 NDC 0049-4910-94 Bottles of 5000 NDC 0049-4910-41 Unit Dose Packages of 100 Store at controlled room temperature, 59° to 86°F (15° to 30°C). ZOLOFT®, Oral Concentrate: ZOLOFT Oral Concentrate is a clear, colorless solution with a menthol scent containing sertraline hydrochloride equivalent to 20 mg of sertraline per mL and 12% alcohol. It is supplied as a 60 mL bottle with an accompanying calibrated dropper. NDC 0049-4940-23 Bottles of 60 mL	HOW SUPPLIED TO BE DETERMINED

INNOVATOR'S INSERT LABELING	PROPOSED INSERT LABELING
Store at controlled room temperature, 59° to 86°F (15° to 30°C).	Store at controlled room temperature 15°-30°C (59°-86°F) (See USP)
Rx only© 2000 Pfizer Inc Distributed by Roerig Division of Pfizer Inc, NY, NY 10017 69-4721-00-6 Revised January 2000	SERTRALINE HYDROCHLORIDE CAPSULES